

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1-71. (Canceled)

72. (Currently amended) A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism comprising:

a clustering module for clustering quantitative trait locus data from a plurality of quantitative trait locus analyses to form a quantitative trait locus interaction map; wherein

each quantitative trait locus analysis in said plurality of quantitative trait locus analyses is performed for a gene in a plurality of genes in the genome of a second species using a genetic marker map and a quantitative trait in order to produce said quantitative trait locus data, wherein, for each quantitative trait locus analysis, said quantitative trait comprises an expression statistic for the gene for which the quantitative trait locus analysis is performed, for each organism in a plurality of organisms of said second species; and wherein

said genetic marker map is constructed from a set of genetic markers associated with said plurality of organisms of said second species; and

an analysis module for analyzing said quantitative trait locus interaction map to identify a gene **G'** in said second species that is associated with a clinical trait **T** exhibited by a first species and said second species, wherein said gene **G'** is an ortholog of a gene **G** in said first species.

73-85. (Canceled)

86. (Currently amended) A computer system for identifying a quantitative trait locus for a complex trait in a first species, wherein the complex trait is exhibited by said first species and a second species, the computer system comprising:

a central processing unit;

a memory, coupled to the central processing unit, the memory storing a classification module[[],] and a genetic analysis module; wherein

the classification module includes instructions for dividing a plurality of organisms of a second species into a plurality of subpopulations using a classification scheme that classifies each organism in said plurality of organisms of said second species into at least one subpopulation in [[of]] said plurality of subpopulations, wherein said classification scheme uses a plurality of cellular constituent measurements from each said organism in said second species; and

the genetic analysis module includes instructions that, for at least one subpopulation in said plurality of subpopulations, performs quantitative genetic analysis on said at least one subpopulation in order to identify said quantitative trait locus in said second species for said complex trait, wherein the quantitative trait locus in said second species is the ortholog of the quantitative trait locus in said first species.

87-125. (Canceled)

126. (Currently amended) A method for confirming [[the]] an association of a query QTL or a query gene in the genome of a second species with a clinical trait T exhibited by said second species, the method comprising:

(a) mapping (i) a region of the genome of a first species that comprises a first QTL abundance quantitative trait loci (eQTL) ~~or a first gene~~ in said first species that is linked to a trait T' exhibited by said first species to (ii) a region of the genome of said second species, wherein said trait T' is indicative of said clinical trait T; and

(b) ~~finding a query QTL or a query gene in said second species that is potentially associated with said trait T, wherein confirming the potential association of said query QTL or said query gene with said clinical trait T is confirmed when said query QTL or said query gene is both (i) linked to said clinical trait T and (ii) is in said region of the genome of said second species.~~

127. (Currently amended) The method of claim 126, the method further comprising, prior to said mapping step (a), a step of finding said first eQTL ~~QTL or said first gene~~ in said first species comprising:

- (i) crossing a first strain and a second strain of said first species in order to obtain a segregating population;
- (ii) stratifying said segregating population into a plurality of subpopulations, wherein a subpopulation in said plurality of subpopulations represents a phenotypic extreme of said trait T';
- (iii) using a plurality of cellular constituent measurements from organisms in the plurality of subpopulations to identify a cellular constituent set that exhibits a cellular constituent measurement pattern associated with said phenotypic extreme;
- (iv) clustering said segregating population based on measurements of said cellular constituent set in organisms in said segregating population to obtain a plurality of population clusters; and
- (v) for at least one population cluster in said plurality of population clusters, performing quantitative genetic analysis on said at least one population cluster in order to find said first eQTL QTL or said first gene in said first species that is linked to said trait T'.

128. (Currently amended) The method of claim 127 wherein said plurality of cellular constituent measurements are transcriptional state measurements or translational state measurements.

129. (Currently amended) The method of claim 127 wherein said plurality of cellular constituent measurements are translational state measurements that are performed using an antibody array or two-dimensional gel electrophoresis.

130. (Original) The method of claim 127 wherein said cellular constituent set comprises a plurality of metabolites and said plurality of cellular constituent measurements are derived by a cellular phenotypic technique.

131. (Currently amended) The method of claim 130 wherein said cellular phenotypic technique comprises a metabolomic technique wherein a plurality of levels of a plurality of metabolites in one or more organisms in said segregating population is measured.

132. (Currently amended) The method of claim 131 wherein a metabolite in said plurality of metabolites ~~comprise~~ comprises an amino acid, a metal, a soluble sugar, or a complex carbohydrate.

133. (Currently amended) The method of claim 127 wherein said plurality of cellular constituent measurements ~~comprise~~ comprises gene expression levels, abundance of mRNA, protein expression levels, or metabolite levels.

134. (Currently amended) The method of claim 126, the method further comprising, prior to said mapping step (a), a step of finding said first eQTL ~~QTL~~ or ~~said first gene~~ in said first species comprising:

- (i) crossing a first strain and a second strain of said first species in order to obtain a segregating population;
- (ii) dividing said segregating population into a plurality of subpopulations using a classification scheme that classifies each organism in said segregating population into at least one ~~of said population in said plurality of subpopulations~~ subpopulations, wherein said classification scheme uses cellular constituent measurements of a plurality of cellular constituents from each said organism; and
- (iii) for at least one subpopulation in said plurality of subpopulations, performing a quantitative genetic analysis on said at least one subpopulation in order to find said first eQTL ~~QTL~~ or ~~said first gene~~ in said first species that is linked to trait T'.

135. (Original) The method of claim 134 wherein said cellular constituent measurements are transcriptional state measurements or translational state measurements.

136. (Original) The method of claim 134 wherein said cellular constituent measurements are translational state measurements that are performed using an antibody array or two-dimensional gel electrophoresis.

137. (Currently amended) The method of claim 134 wherein said plurality of cellular constituents comprise a plurality of metabolites ~~and said plurality of cellular constituent measurements are derived by~~ measured using a cellular phenotypic technique.

138. (Currently amended) The method of claim 137 wherein said cellular phenotypic technique comprises a metabolomic technique wherein ~~a plurality of~~ levels of a plurality of metabolites in each said organism is measured.

139. (Currently amended) The method of claim 138 wherein said plurality of metabolites ~~comprise~~ comprises an amino acid, a metal, a soluble sugar, or a complex carbohydrate.

140. (Original) The method of claim 134 wherein said cellular constituent measurements of said plurality of cellular constituents comprise gene expression levels, abundance of mRNA, protein expression levels, or metabolite levels.

141. (Currently amended) The method of claim 126, the method further comprising, prior to said mapping step (a), a step of finding said first eQTL QTL or ~~said first gene~~ in said first species comprising:

- (i) generating a set of congenic organisms that span all or a portion of the genome of said first species using a background strain and a donor strain; and
- (ii) identifying those strains in said set of congenic organisms that exhibit trait T'.

142. (Original) The method of claim 126 wherein said mapping step (a) is based upon a syntenic map between said first species and said second species.

143. (Original) The method of claim 126 wherein said finding step (b) comprises performing quantitative genetic analysis on a population of said second species.

144. (Original) The method of claim 126 wherein said clinical trait T is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine, nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

145. (Currently amended) The method of claim 126 wherein said quantitative genetic analysis is performed using a method that uses one or more techniques selected from the group consisting of (i) linkage analysis, (ii) a quantitative trait locus (QTL) analysis ~~that uses~~ using a plurality of cellular constituent measurements as a phenotypic trait, and (iii) an association analysis.

146. (Currently amended) The method of claim 145 wherein said first eQTL QTL is represented by a lod score that is greater than 3.0.

147. (Currently amended) The method of claim 145 wherein said first eQTL QTL is represented by a lod score that is greater than 4.0.

148. (Currently amended) The method of claim 127 wherein said quantitative genetic analysis is performed using a method that uses one or more techniques selected from the group consisting of (i) linkage analysis, (ii) a quantitative trait locus (QTL) analysis ~~that uses~~ using a plurality of cellular constituent measurements as a phenotypic trait, and (iii) an association analysis.

149. (Currently amended) The method of claim 148 wherein said first eQTL QTL is represented by a lod score that is greater than 3.0.

150. (Currently amended) The method of claim 148 wherein said first eQTL QTL is represented by a lod score that is greater than 4.0.

151. (Currently amended) The method of claim 134 wherein said quantitative genetic analysis is performed using a method that uses one or more techniques selected from the group consisting of (i) linkage analysis, (ii) a quantitative trait locus (QTL) analysis ~~that uses~~ using a plurality of cellular constituent measurements as a phenotypic trait, and (iii) an association analysis.

152. (Currently amended) The method of claim 151 wherein said first eQTL QTL is represented by a lod score that is greater than 3.0.

153. (Currently amended) The method of claim 151 wherein said first eQTL QTL is represented by a lod score that is greater than 4.0.

154. (Original) The method of claim 126 wherein said second species is human.

155. (Original) The method of claim 126 wherein said clinical trait T is obesity and said trait T' is high density lipoprotein level, low density lipoprotein level, very low density lipoprotein level, free fatty acid level, fat pad mass, or weight/height ratio.

156. (Original) The method of claim 126 wherein said region of the genome of said first species is a portion of a chromosome.

157. (Original) The method of claim 126 wherein said region of the genome of said first species is less than 100 centiMorgans.

158. (Original) The method of claim 126 wherein said region of the genome of said first species is less than 10 centiMorgans.

159. (Original) The method of claim 126 wherein said region of the genome of said first species is less than 5 centiMorgans.

160-167. (Canceled)

168. (Original) A method of identifying a molecular target for a second trait in a second species, the method comprising:

(a) identifying a first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population, wherein each member of said segregating population is a member of a first species and wherein said second trait in said second species corresponds to said first trait in said first species;

(b) mapping said first gene in said first species to a corresponding locus in the genome of the second species; and

(c) determining whether a marker or a haplotype in said corresponding locus in the genome of the second species associates with said second trait, wherein, when said marker or

said haplotype associates with said second trait in said second species, said locus is identified as said molecular target.

169. (Original) The method of claim 168 wherein said marker or said haplotype is in a second gene in said corresponding locus and said second gene is identified as said molecular target.

170. (Original) The method of claim 169 wherein said first gene and said second gene are orthologous.

171. (Original) The method of claim 168 wherein said identifying said first gene in said segregating population that is causal for said first trait exhibited by all or a portion of said segregating population comprises:

(a) identifying a test gene in said first species that has at least one abundance quantitative trait locus (eQTL) coincident with a respective clinical quantitative trait locus (cQTL) for said first trait; and

(b) testing, for one or more respective eQTL in said at least one eQTL, whether (i) the genetic variation of said eQTL across said segregating population and (ii) the variation of the first trait across said segregating population are correlated conditional on an abundance pattern of the test gene across said segregating population,

wherein, when the genetic variation of (1) said one or more respective eQTL tested in step (b) and (2) the variation of the first trait across said segregating population are correlated conditional on an abundance pattern of the test gene across said segregating population, said test gene is identified as said first gene.

172. (Original) The method of claim 168 wherein said second species is mammalian.

173. (Original) The method of claim 168 wherein said second species is human.

174. (Original) The method of claim 168 wherein said second trait is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine,

nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

175. (Original) The method of claim 168 wherein said molecular target is a gene.

176. (Original) The method of claim 168 wherein said molecular target is an exon, an intron, or a regulatory element of a gene.

177. (Original) The method of claim 168 wherein said marker is a single nucleotide polymorphism, a microsatellite marker, a restriction fragment length polymorphism, a short tandem repeat, a DNA methylation marker, a sequence length polymorphism, a random amplified polymorphic DNA, an amplified fragment length polymorphisms, or a simple sequence repeat.

178. (Original) A method of identifying a molecular target for a second trait in a second species, the method comprising:

(a) identifying a first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population, wherein each member of said segregating population is a member of a first species and wherein said second trait in said second species corresponds to said first trait in said first species;

(b) identifying a locus in the genome of the second species that is (1) linked to said second trait and (2) maps to the position in the genome of said first species where said first gene resides; and

(c) determining whether a marker or a haplotype in said corresponding locus in the genome of the second species associates with said second trait, wherein, when said marker or said haplotype associates with said second trait in said second species, said locus is identified as said molecular target.

179. (Original) The method of claim 178 wherein said marker or said haplotype is in a second gene in said corresponding locus and said second gene is identified as said molecular target.

180. (Original) The method of claim 179 wherein said first gene and said second gene are orthologous.

181. (Original) The method of claim 178 wherein said identifying said first gene in said segregating population that is causal for said first trait exhibited by all or a portion of said segregating population comprises:

(a) identifying a test gene in said first species that has at least one abundance quantitative trait locus (eQTL) coincident with a respective clinical quantitative trait locus (cQTL) for said first trait; and

(b) testing, for one or more respective eQTL in said at least one eQTL, whether (i) the genetic variation of said eQTL across said segregating population and (ii) the variation of the first trait across said segregating population are correlated conditional on an abundance pattern of the test gene across said segregating population,

wherein, when the genetic variation of (1) said one or more respective eQTL tested in step (a) and (2) the variation of the first trait across said segregating population are correlated conditional on an abundance pattern of the test gene across said segregating population, said test gene is identified as said first gene.

182. (Original) The method of claim 178 wherein said second species is mammalian.

183. (Original) The method of claim 178 wherein said second species is human.

184. (Original) The method of claim 178 wherein said second trait is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine, nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

185. (Original) The method of claim 178 wherein said molecular target is a gene.

186. (Original) The method of claim 178 wherein said molecular target is an exon, an intron, or a regulatory element of a gene.

187. (Original) The method of claim 178 wherein said marker is a single nucleotide polymorphism, a microsatellite marker, a restriction fragment length polymorphism, a short tandem repeat, a DNA methylation marker, a sequence length polymorphism, a random amplified polymorphic DNA, an amplified fragment length polymorphisms, or a simple sequence repeat.

188. (Original) A method of identifying a molecular target for a second trait in a second species, the method comprising:

(a) identifying a first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population, wherein each member of said segregating population is a member of a first species and wherein said second trait in said second species corresponds to said first trait in said first species; and

(b) identifying a second gene in the genome of the second species that is orthologous to said first gene and in which (i) the variation of the abundance of the second gene across biological samples taken from a plurality of members of said second species and (ii) the variation of the second trait across said plurality of members of said second species are associated, wherein

said second gene is identified as said molecular target.

189. (Original) The method of claim 188, the method further comprising:

validating said second gene by determining whether a marker or a haplotype in said second gene associates with said second trait, wherein, when said marker or said haplotype associates with said second trait in said second species, said second gene is validated.

190. (Original) The method of claim 188 wherein said identifying said first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population comprises:

(a) identifying a test gene in said first species that has at least one abundance quantitative trait locus (eQTL) coincident with a respective clinical quantitative trait locus (cQTL) for said first trait; and

(b) testing, for one or more respective eQTL in said at least one eQTL, whether (i) the genetic variation of said eQTL across said segregating population and (ii) the variation of the first trait across said segregating population are correlated conditional on an abundance pattern of the test gene across said segregating population,

wherein, when the genetic variation of (1) said one or more respective eQTL tested in step (b) and (2) the variation of the first trait across said segregating population are correlated conditional on an abundance pattern of the test gene across said segregating population, said test gene is identified as said first gene.

191. (Original) The method of claim 188 wherein said second species is mammalian.

192. (Original) The method of claim 188 wherein said second species is human.

193. (Original) The method of claim 188 wherein said second trait is asthma, ataxia telangiectasia, bipolar disorder, cancer, common late-onset Alzheimer's disease, diabetes, heart disease, hereditary early-onset Alzheimer's disease, hereditary nonpolyposis colon cancer, hypertension, infection, maturity-onset diabetes of the young, mellitus, migraine, nonalcoholic fatty liver, nonalcoholic steatohepatitis, non-insulin-dependent diabetes mellitus, obesity, polycystic kidney disease, psoriasis, schizophrenia, or xeroderma pigmentosum.

194. (Original) The method of claim 188 wherein said marker is a single nucleotide polymorphism, a microsatellite marker, a restriction fragment length polymorphism, a short tandem repeat, a DNA methylation marker, a sequence length polymorphism, a random amplified polymorphic DNA, an amplified fragment length polymorphisms, or a simple sequence repeat.

195. (Original) A computer system for identifying a molecular target for a second trait in a second species, the computer system comprising:

a central processing unit;

a memory, coupled to the central processing unit, the memory storing:

instructions for identifying a first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population, wherein each member of

said segregating population is a member of a first species and wherein said second trait in said second species corresponds to said first trait in said first species;

instructions for mapping said first gene in said first species to a corresponding locus in the genome of the second species; and

instructions for determining whether a marker or a haplotype in said corresponding locus in the genome of the second species associates with said second trait.

196. (Original) A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism comprising:

instructions for identifying a first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population, wherein each member of said segregating population is a member of a first species and wherein said second trait in said second species corresponds to said first trait in said first species;

instructions for mapping said first gene in said first species to a corresponding locus in the genome of the second species; and

instructions for determining whether a marker or a haplotype in said corresponding locus in the genome of the second species associates with said second trait.

197. (Original) A computer system for identifying a molecular target for a second trait in a second species, the computer system comprising:

a central processing unit;

a memory, coupled to the central processing unit, the memory storing:

instructions for identifying a first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population, wherein each member of said segregating population is a member of a first species and wherein said second trait in said second species corresponds to said first trait in said first species;

instructions for identifying a locus in the genome of the second species that is (1) linked to said second trait and (2) maps to the position in the genome of said first species where said first gene resides; and

instructions for determining whether a marker or a haplotype in said corresponding locus in the genome of the second species associates with said second trait.

198. (Original) A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism comprising:

instructions for identifying a first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population, wherein each member of said segregating population is a member of a first species and wherein said second trait in said second species corresponds to said first trait in said first species;

instructions for identifying a locus in the genome of the second species that is (1) linked to said second trait and (2) maps to the position in the genome of said first species where said first gene resides; and

instructions for determining whether a marker or a haplotype in said corresponding locus in the genome of the second species associates with said second trait.

199. (Original) A computer system for identifying a molecular target for a second trait in a second species, the computer system comprising:

a central processing unit;

a memory, coupled to the central processing unit, the memory storing:

instructions for identifying a first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population, wherein each member of said segregating population is a member of a first species and wherein said second trait in said second species corresponds to said first trait in said first species; and

instructions for identifying a second gene in the genome of the second species that is orthologous to said first gene and in which (i) the variation of the abundance of the second gene across biological samples taken from a plurality of members of said second species and (ii) the variation of the second trait across said plurality of members of said second species are associated.

200. (Original) A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism embedded therein, the computer program mechanism comprising:

instructions for identifying a first gene in a segregating population that is causal for a first trait exhibited by all or a portion of said segregating population, wherein each member of said segregating population is a member of a first species and wherein said second trait in said second species corresponds to said first trait in said first species; and

instructions for identifying a second gene in the genome of the second species that is orthologous to said first gene and in which (i) the variation of the abundance of the second gene across biological samples taken from a plurality of members of said second species and (ii) the variation of the second trait across said plurality of members of said second species are associated.

201. (New) A computer system for confirming the association of a query QTL or a query gene in the genome of a second species with a clinical trait T exhibited by said second species, the computer system comprising:

a central processing unit;

a memory, coupled to the central processing unit, the memory storing:

instructions for mapping (i) a region of the genome of a first species that comprises a first abundance quantitative trait loci (eQTL) in said first species that is linked to a trait T' exhibited by said first species to (ii) a region of said genome of said second species, wherein said trait T' is indicative of the clinical trait T; and

instructions for confirming the association of said query QTL or said query gene with said clinical trait T when said query QTL or said query gene is both (i) linked to said clinical trait T and (ii) is in said region of the genome of said second species.

202. (New) A computer program product for use in conjunction with a computer system, the computer program product comprising a computer readable storage medium and a computer program mechanism, for confirming the association of a query eQTL in the genome of a second species with a clinical trait T exhibited by said second species, embedded therein, the computer program mechanism comprising:

instructions for mapping (i) a region of the genome of a first species that comprises a first abundance quantitative trait loci (eQTL) in said first species that is linked to a trait T' exhibited by said first species to (ii) a region of the genome of said second species, wherein said trait T' is indicative of the clinical trait T; and

instructions for confirming the association of said query QTL or said query gene with said clinical trait T when said query QTL or said query gene is both (i) linked to said clinical trait T and (ii) is in said region of the genome of said second species.